
2014 Space Radiation Standing Review Panel

Research Plan Reviews for:

The Risk Of Cardiovascular Disease and Other Degenerative Tissue Effects From Radiation Exposure

Status Reviews for:

The Risk of Acute and Late Central Nervous System Effects from Radiation Exposure,

The Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs), and

The Risk of Radiation Carcinogenesis

Final Report

I. Executive Summary and Overall Evaluation

The 2014 Space Radiation Standing Review Panel (from here on referred to as the SRP) participated in a WebEx/teleconference with members of the Space Radiation Program Element, representatives from the Human Research Program (HRP), the National Space Biomedical Research Institute (NSBRI), and NASA Headquarters on November 21, 2014 (list of participants is in Section XI of this report). The SRP reviewed the updated Research Plan for the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure (Degen Risk). The SRP also received a status update on the Risk of Acute and Late Central Nervous System Effects from Radiation Exposure (CNS Risk), the Risk of Acute Radiation Syndromes Due to Solar Particle Events (ARS Risk), and the Risk of Radiation Carcinogenesis (Cancer Risk).

The SRP thought the teleconference was very informative and that the Space Radiation Program Element did a great job of outlining where the Element is with respect to our state of knowledge on the risks of carcinogenesis, central nervous system effects, and the risk of cardiovascular disease and other degenerative tissue effects from exposure to space radiation. The SRP was impressed with the quality of research that is being conducted and the progress the Space Radiation Program Element has made in the past year. While much work has been done, the SRP had a few remaining questions regarding the broad applicability of these findings to a manned deep space mission (in terms of cognitive function, the paradigms were still hippocampal based and also using Alzheimer disease models).

The SRP believes that NASA should consider developing an approach to follow astronauts long-term (beyond retirement) for potential side-effects/risks of space exposure that may be unknown. Radiation toxicities often occur decades after exposure, and potential consequences would be missed if intensified exams stop after retirement of the astronauts. In addition, while cancer is one consequence of radiation exposure that is monitored, potential other side effects (CNS, Alzheimer Disease, loss of cognitive function, etc.) are not included in long-term studies and would be missed. Inclusion of long-term data would be of benefit to the astronauts themselves who have given their service to the corps but also to future astronauts and the future of space exploration.

The NASA HRP is embarking on an interesting twin study that will examine at least 14 parameters (microbiome, telomere length, methylation of DNA, etc.) in astronauts, one of whom

will be in space for over a year while his identical twin brother remains on Earth. The SRP believes that some mechanism to allow for relevant data from those studies to be passed on to animal studies in order to examine biomarkers, mechanisms of responses, etc., should be considered.

The translation of experimental data to applications in humans is often difficult and is usually accomplished through a variety of different efforts including animal work, modeling, and others. The SRP believes that a more thorough consideration and discussion about how NASA plans to accomplish this translation would be important in establishing how risks from space radiation can be properly assessed.

The SRP noticed that oxygen (O_2) tension was not considered as a risk factor. Although the short-term effects of breathing high O_2 concentrations are well known at least for low Linear Energy Transfer (LET) radiation exposure and there is strong evidence that O_2 tension is tightly controlled in the human body, there is little information on physiological effects of long-term exposure to high O_2 concentrations and lower than one atmosphere pressure. In the summary of exploration atmospheres provided to the SRP it is stated that O_2 levels in the 85 to 100% range will be used for expected extensive extravehicular activities (EVAs) and that the habitat may be at 34% O_2 for periods prior to EVAs to allow for preparation for EVA. It is possible NASA has examined this issue in other HRP Elements. However, effects of long-term high O_2 tension at lower than one atmosphere on the blood system, the CNS system, and the microbiota of the intestinal system should be considered as possible organs that may respond in as yet unknown ways. This is not only an issue of possible high O_2 effects but possibly hypoxic effects in tissues during long EVAs. Simple Oxygen Enhancement Ratio (OER) usually related to cell killing effects is not the only issue here. The issue, as is being found, for example in CNS, is the long-term effects that may be subtle at first but have long-term consequences to a person who has traveled in deep space and/or spent time on a planet or asteroid and thus been exposed to low fluency HZE particles and high energy protons for long periods of time. Hypoxia would lessen the effect of radiation exposure. It may be worth at least considering possible changes in risk that EVAs with high oxygen tension might cause and what possible changes in risk the level of hypoxia and length of time of hypoxic conditions happens and in what organs it may happen.

The SRP discussed the general issue of “countermeasures” and there was some concern voiced that this term was a “catchall” for everything from shielding, to diet and rescue modules. The SRP recommends that the rapid development of radio-mitigators (funded by the Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID)) against acute effects of radiation for low LET radiations should be examined by NASA and thought given to inclusion of limited basic studies to determine if any of these will work in a proton or HZE environment against both acute, cancerous and degenerative effects of deep space radiations. Some of these are now undergoing the Food and Drug Administration (FDA) approval process and this may be the time to find out if they may be useful or not.

The SRP noted some discussion of “integration” between some HRP Elements on some tasks. While the SRP realizes there may be limited opportunities for useful integration between HRP Elements for a number of reasons, the one area that may benefit the overall development of risk

models is to look at translating clinical studies on Earth, both of astronauts and radiotherapy patients. With basic science, serious efforts should be made, where possible, to integrate or at least compare the data on similar endpoints or organs to examine if the human condition is actually replicated adequately by the animal and cellular models in the peer reviewed science; if not it will be important to solicit efforts to bridge this gap.

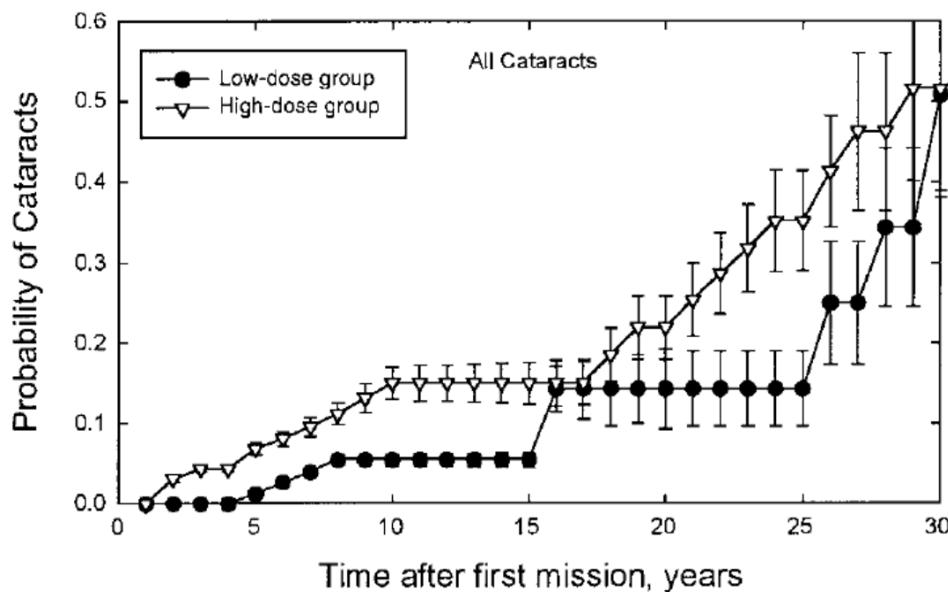
The SRP is aware that it is challenging to have in-person meetings with the Space Radiation Program Element every year, but there are many difficulties associated with carrying out a review by WebEx/teleconference. The SRP encourages the HRP to schedule in-person meetings, as frequently as possible, to enhance deliberation by the SRP, as well as interaction between SRP members and HRP staff.

II. Critique of Gaps and Tasks for the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure

The SRP notes that NASA has put together a very robust series of tasks to address the gaps in our knowledge related to the Degen Risk. Overall, the SRP is impressed with the portfolio of tasks that have been awarded in this effort and the progress made thus far.

The SRP notes that the current gaps are appropriate but may need to be better characterized in terms of: 1) microvascular function and immune modulation, 2) the processes of accelerated aging and 3) organ-organ interactions, such as cardio-renal, CNS-immune, and other similar systems. Most of the current tasks are relevant for space travel to date, but the information may need to be better tailored, including radiation spectrum and target organs at risk, for a Mars mission. The SRP also believes that although the current information is valuable, it must be validated in astronauts of existing missions to ensure that the model based research is applicable to human conditions.

The SRP has concerns that the data on the graph below (p. 64 of the 2014 Space Radiation Program Element presentation to the SRP: Chylack et al. Radiat Res 2012¹) are meaningless without appropriate controls. It could be the case that the data for age-matched astronauts that were not exposed to space radiation would lay above the points shown indicating that exposure to space radiation protects against cataracts. The SRP does not understand why a graph like this was presented without controls. When asked if there were a control group, the SRP was told yes. But, why aren't the control data shown? Also, what were the actual doses given? At least a range should be given. Also, what does each individual symbol represent?



Gaps and Tasks:

Degen - 1: How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?

- The SRP thinks this Gap is relevant and appropriate.
- The SRP thinks issue specific changes in multiple organs can be tracked more cost-effectively by common model exposures at graded doses with appropriate radiation spectrum and the different tissues, allocated in a competitive fashion to different expert groups and analyzed according to preplanned protocols.
- The endpoints that can be measured include macrovascular and microvascular function, vascular reactivity, free radical production, microvascular inflammation, and associated biomarker changes.
- The SRP thinks the inter-organ cross talk should also be evaluated in the models wherever possible.
- The SRP thinks equivalent follow up of human radiation exposure should also be done to validate these basic model estimations.

Tasks:

- Early Markers of Space-Radiation Induced Human Cataractogenesis – Completed Task
- Effects of Estrogen on Cataract Induction After Exposure to High LET Radiation – Completed Task
- Evaluation of Space Radiation-induced Myocardial and BM-derived EPC Damage and Assessment of Associated Long-term Degenerative Cardiovascular Risks – PI: David Goukassian, M.D., Ph.D. – Genesys Research Institute
- Human endothelial cells in 2-D and 3-D systems; non-cancer effects and space-related radiations – Completed Task
- Ionizing Radiation and its Effects on Cardiovascular Function in the Context of Space Flight – Completed Task
- Mechanisms, early events, and dose dependence of radiation-induced atherosclerosis –

PI: Dennis Kucik, M.D., Ph.D. – University of Alabama at Birmingham

- Spaceflight effects on the mouse retina: Histological, gene expression and epigenetic changes after flight on STS-135 – Completed Task
- Combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rat eyes – Completed Task
- Low Dose Radiation Cataract – Completed Task
- The Relation Between Cognitive Injury, Network Stability, and Epigenetic Change Following Exposure to Space Radiation – PI: Jacob Raber, Ph.D. – Oregon Health & Science University
- Ground Based Research to develop and validate mechanistic models for Circulatory Disease from Space Radiation Phase 1 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Circulatory and other Degenerative Diseases from Space Radiation Phase 2 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget
- A Metabolomics and Mouse Models Approach to Study Inflammatory and Immune Responses to Radiation – PI: Albert Fornace, M.D. – Lombardi Comprehensive Cancer Center
- Oxidative Stress and Skeletal Health with Low Dose, Low LET Ionizing Radiation – PI: Ruth Globus, Ph.D. – NASA Ames Research Center
- Radiation-Induced Early Changes in Gene and Protein Expression, Lipid Oxidative States, and Vascular Function Related to Atherosclerosis – PI: Dennis Kucik, M.D., Ph.D. – University of Alabama at Birmingham
- Charged Particle Effects on the Ovary – PI: Ulrike Luderer, M.D., Ph.D. – University of California, Irvine
- The Role of Oxidative Stress and Inflammation on Synaptic Functions After Exposure to Space Radiation – PI: Susanna Rosi, Ph.D. – University of California, San Francisco
- The Effect of High LET Radiation on Differentiation and Tumorigenesis in the Human Hematopoietic System: Modeling in vitro and in vivo for Risk Assessment – PI: Lubomir Smilénov, Ph.D. – Columbia University
- Development of a Flow-Perfused and Immunocompetent 3-D Vascular Model for Radiation Risk Assessment of Cardiovascular Disease and Countermeasure Screening – PI: Zarana Patel, Ph.D. – NASA Johnson Space Center

Degen - 2: What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens and other tissue systems? What surrogate endpoints do they suggest?

- The SRP thinks this Gap is relevant and appropriate.
- Radiation induced free radical production can in turn activate the immune-inflammatory system, leading to local metabolic/mitochondrial dysfunction, accelerated cell deaths and increased fibrosis.
- All of this is compatible with an accelerated aging process.
- The SRP thinks endpoints collected should reflect steps in this pathway, and mitigation strategies tested to address some of these mechanisms.

Tasks:

- Early Markers of Space-Radiation Induced Human Cataractogenesis – Completed Task
- Effects of Estrogen on Cataract Induction After Exposure to High LET Radiation – Completed Task
- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- Human endothelial cells in 2-D and 3-D systems; non-cancer effects and space-related radiations – Completed Task
- Ionizing Radiation and its Effects on Cardiovascular Function in the Context of Space Flight – Completed Task
- Mechanisms, early events, and dose dependence of radiation-induced atherosclerosis – PI: Dennis Kucik, M.D., Ph.D. – University of Alabama at Birmingham
- Spaceflight effects on the mouse retina: Histological, gene expression and epigenetic changes after flight on STS-135 – Completed Task
- Effects of Space Radiation on Hippocampal-Dependent Learning and Neuropathology in Wild-Type and Alzheimer's Disease Transgenic Mice – PI: Lee Goldstein, M.D., Ph.D. – Boston University
- Combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rat eyes – Completed Task
- Precise Assessment of Prevalence and Progression of Lens Opacities in Astronauts as a Function of Radiation Exposure During Space Flight and Development of Improved Routine Clinical Assessment of Ocular Lens Status – Completed Task
- Mechanisms of Ocular Cataracts – Completed Task
- Effects of Space Radiation on Long-Term Synaptic Plasticity and Neurogenesis in Normal and Alzheimer's Disease Transgenic Mice – PI: Patric Stanton, Ph.D. – New York Medical College
- The Relation Between Cognitive Injury, Network Stability, and Epigenetic Change Following Exposure to Space Radiation – PI: Jacob Raber, Ph.D. – Oregon Health & Science University
- Ground Based Research to develop and validate mechanistic models for Circulatory Disease from Space Radiation Phase 1 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Circulatory and other Degenerative Diseases from Space Radiation Phase 2 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget
- The Effects of Space Radiation on Stem Cells and Vascular and Cardiac Disease – PI: Ian McNiece, Ph.D. – University of Texas MD Anderson Cancer Center
- A Metabolomics and Mouse Models Approach to Study Inflammatory and Immune Responses to Radiation – PI: Albert Fornace, M.D. – Lombardi Comprehensive Cancer Center
- Oxidative Stress and Skeletal Health with Low Dose, Low LET Ionizing Radiation – PI: Ruth Globus, Ph.D. – NASA Ames Research Center
- Non-Invasive Early Detection and Molecular Analysis of Low X-ray Dose Effects in the

Lens – PI: Lee Goldstein, M.D., Ph.D. – Boston University

- Radiation-Induced Early Changes in Gene and Protein Expression, Lipid Oxidative States, and Vascular Function Related to Atherosclerosis – PI: Dennis Kucik, M.D., Ph.D. – University of Alabama at Birmingham
- Charged Particle Effects on the Ovary – PI: Ulrike Luderer, M.D., Ph.D. – University of California, Irvine

Degen - 3: What are the progression rates and latency periods for degenerative risks, and how do progression rates depend on age, gender, radiation type, or other physiological or environmental factors?

- The SRP thinks this Gap is relevant and appropriate.
- Radiation induced free radical damage of proteins is cumulative, but can be mitigated by host's intrinsic systems of protein quality control and damaged protein recycling processes. However, these processes are aging and background risk factor dependent.
- The efficiencies of the host defense system, including appropriate protein replacement and turnover (through ubiquitin-proteasomal degradation or autophagy), and cell repair and regeneration following exposure to appropriate spectrum and duration of radiation will be important.
- The SRP thinks how these processes are affected by the background risk factors such as aging, hypercholesterolemia, etc., should be characterized.
- During the WebEx/teleconference presentations, the SRP was told the O₂ concentration expected in the space travel modules and space suits may be set as high as 34% as there have been cases of hypoxia when using lower O₂ in ambient air. The SRP has discussed this before and because there is a strong relationship between O₂ concentration and radiation effects due to the Oxygen Enhancement Ratio (that can be as high as 3) and this being directly related to free radical production and removal, the SRP believes there should be an analysis of this potential risk and possible inclusion of the O₂ concentration in future calls to determine experimentally if it is of concern for degenerative risks.

Tasks:

- Effects of Estrogen on Cataract Induction After Exposure to High LET Radiation – Completed Task
- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- Evaluation of Space Radiation-induced Myocardial and BM-derived EPC Damage and Assessment of Associated Long-term Degenerative Cardiovascular Risks – PI: David Goukassian, M.D., Ph.D. – Genesys Research Institute
- Effects of Space Radiation on Hippocampal-Dependent Learning and Neuropathology in Wild-Type and Alzheimer's Disease Transgenic Mice – PI: Lee Goldstein, M.D., Ph.D. – Boston University
- Effects of Space Radiation on Long-Term Synaptic Plasticity and Neurogenesis in Normal and Alzheimer's Disease Transgenic Mice – PI: Patric Stanton, Ph.D. – New York Medical College
- Individual Differences in the Neurochemical and Behavioral Response to Exposure to Protons and HZE Particles – PI: Bernard Rabin, Ph.D. – University of Maryland, Baltimore County

- Ground Based Research to develop and validate mechanistic models for Circulatory and other Degenerative Diseases from Space Radiation Phase 2 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget
- Charged Particle Effects on the Ovary – PI: Ulrike Luderer, M.D., Ph.D. – University of California, Irvine

Degen - 4: How does individual susceptibility including hereditary pre-disposition alter degenerative tissue risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?

- The SRP thinks this Gap is relevant and appropriate.
- Processes such as inflammatory potential, aging, cell repair and regenerative capacity are all affected by genetic programming and environmental risk exposure. However, information to date suggests that environmental risk factors are much more influential in a quantitative fashion, thus this would likely be the most fruitful area for exploration.

Tasks:

- Effects of Intestinal Microflora on High-LET Radiation Mediated Toxicity and Genomic Instability – Completed Task
- Effect of Space Radiation on degenerative tissue disease, genetic Instability and Oxidative DNA Damage in Ataxia Telangiectasis Deficient Mice – Completed Task
- Effects of Space Radiation on Long-Term Synaptic Plasticity and Neurogenesis in Normal and Alzheimer's Disease Transgenic Mice – PI: Patric Stanton, Ph.D. – New York Medical College
- Individual Differences in the Neurochemical and Behavioral Response to Exposure to Protons and HZE Particles – PI: Bernard Rabin, Ph.D. – University of Maryland, Baltimore County
- Ground Based Research to develop and validate mechanistic models for Circulatory and other Degenerative Diseases from Space Radiation Phase 2 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget
- Charged Particle Effects on the Ovary – PI: Ulrike Luderer, M.D., Ph.D. – University of California, Irvine

Degen - 5: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts?

How can human epidemiology data best support these procedures or models?

- The SRP thinks this Gap is relevant and appropriate.
- The SRP thinks the biological responses in terms of dose relationship to exposure and whether there is a threshold response effect should be determined for a specific organ system. The information will then need to be cross-validated in humans based on clinical radiation exposure information, and modifications based on modulating factors such as risk factors, age, gender, etc.

Tasks:

- Ground Based Research to develop and validate mechanistic models for Circulatory Disease from Space Radiation Phase 1 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Circulatory and other Degenerative Diseases from Space Radiation Phase 2 – Unfunded Task/Not within Current Budget
- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget

Degen - 6: What are the most effective biomedical or dietary countermeasures to degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?

- The SRP thinks this Gap is relevant and appropriate.
- Exercise is currently the best measure to mitigate risk, because it is so far the most effective way to accelerate protein quality control, and replace damaged proteins with newly synthesized versions. This process is likely also dependent on microvascular blood flow, redox balance and metabolic efficiency. All of the latter are also improved by exercise.
- Other anti-aging measures such as brain stimulation and social interactions are also important potential strategies though less proven.
- The SRP thinks the most protective diet to date is the Mediterranean diet, rich in anti-oxidants and balanced in nutrients. However, trying to simulate this diet in space may be challenging.
- These mechanisms are likely synergistic.

Tasks:

- Effects of Estrogen on Cataract Induction After Exposure to High LET Radiation – Completed Task
 - The SRP thinks that cataracts may represent a good biomarker for cardiovascular effects. The advantage is that they can be quantified easily using non-invasive technology and documented over time for each individual. However, looking at the retina microvasculature is also relatively simple and may represent an even more relevant approach.
 - New data on cataract incidence imply stochastic radiation effects in its development. The SRP thinks this should be further investigated. In the formulation of the task, it will be useful to leave open the possibility that cataract is a deterministic radiation effect – as it was considered for many years now. However, the task should also include investigation of the possible contribution of stochastic effects and should attempt to analyze existing, or to generate new, solid data on this question. Also, the alternative that both stochastic and deterministic effects contribute to cataract development will need to be considered and appropriately incorporated in the task. Finally, the possibility that separation between stochastic and deterministic effects is operational and may not be substantiated by fundamentally different mechanisms will also need to be entertained in the task and possibly incorporated in mechanistic models describing

the incidence of the condition.

- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget

Degen - 7: Are there significant synergistic effects from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?

- The SRP thinks this Gap is relevant and appropriate.
- Stress exposure generates free radicals and accelerates metabolic process that would accelerate and magnify the effect from space radiation.
- Inflammatory cell homing could be affected by stress and microgravity and may further be triggered for greater response in the presence of radiation.
- Cell loss and fibrosis are key areas of chronic tissue modification that has been well studied.

Tasks:

- Simulated Microgravity and Radiation-Induced Bone Degeneration: Oxidative Stress- and p53-Dependent Mechanisms – Completed Task
- Evaluation of the combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rats – Completed Task
- Spaceflight effects on the mouse retina: Histological, gene expression and epigenetic changes after flight on STS-135 – Completed Task
- Combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rat eyes – Completed Task
- Individual Genetic Susceptibility – Completed Task
- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget
- Effects of high dietary heme iron and radiation on cardiovascular function (Radiation/Iron, CVD-Westby, Completed) – Completed Task
- Defining the relationship between biomarkers of oxidative and inflammatory stress and atherosclerosis risk in astronauts during and after long-duration spaceflight (Cardio Ox-Platts, Active) – PI: Steven Platts, Ph.D. – NASA Johnson Space Center
- Combined Effects of Space Radiation and Microgravity on the Function of Human Capillaries and the Endothelial Barrier: Implications for Degenerative Disorders – PI: Peter Grabham, Ph.D. – Center for Radiological Research

Degen - 8: Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?

- The SRP thinks this Gap is relevant and appropriate.
- Clinical validation of radiation treatment and smoking effects on tissue injury should be conducted in the right context with relevant exposures and endpoints.
- The SRP thinks rat models of radiation exposure and simulated smoking exposure should be done.

- Free radical excess together with radiation exposure as proxy of smoking mediated damage.

Task:

- Ground Based Research to develop and validate mechanistic models for Degenerative Tissue Risks from Space Radiation Phase 3 – Unfunded Task/Not within Current Budget

III. Discussion on the strengths and weaknesses of the IRP and identify remedies for the weaknesses, including answering these questions:

- A. Are the Risks addressed in a comprehensive manner?
 - The SRP notes that the Risks are addressed in a comprehensive manner.
- B. Are there areas of integration across HRP disciplines that are not addressed that would better address the Degen Risk?
 - Regarding integration across the HRP disciplines, the SRP suggested that NASA consider studies examining whether diet (e.g., antioxidants) affects incidence of cardiovascular disease.
 - The SRP thinks integrated cross-learning in different organs and tissues are likely to be useful for overall comprehensive monitoring and protection.

IV. Evaluation of the progress on the Degen Risk Research Plan since the 2013 SRP meeting

- At the last SRP meeting, the SRP recommended that some shift in emphasis be made for expanding the research into central nervous and cardiovascular systems even at the expense of research into the risk of carcinogenesis. Based on what was presented this year, the SRP is pleased that this shift is being made.
- With regard to assessing cardiovascular effects in mouse models, there have been findings indicating that understanding the role of damage to the kidney following whole body irradiation is essential. The SRP would emphasize this in future research on this topic.
- There have also been observations illustrating the role of reactive oxygen species (ROS) in contributing especially to effects on the central nervous and cardiovascular systems. Thus, examination of the ability of anti-oxidants on suppressing these effects is warranted. This could be done using appropriate mouse models.

V. Additional Comments regarding the CNS Risk Status Review

- The SRP is in agreement that the unique CNS effects of exposure to high LET radiation in different rat and mouse models (many of which are inbred) is important and should be followed up with studies to examine the mechanisms underlying these effects. However, this also represents a potential problem as to how NASA will

utilize this information to determine the actual risk for HZE-induced CNS effects. It will be critical to determine the most appropriate model(s) for determining risk for CNS effects in human astronauts (i.e., outbred, collaborative cross...?).

- Relatedly, given that astronauts will likely have unique and individual susceptibility to the effects of high LET exposure on the CNS, it will be important to consider models in which individual variability can be assessed and utilized to more effectively determine risk.
- Finally, given increasing evidence that the CNS is impacted by a wide variety of interactions with other organ systems (immune, vascular, microbiome, etc.) and disease states (stress, infection, etc.), it will be essential to collect information regarding the influence of these interactions and potential countermeasures that could be utilized to reduce risk across these domains.

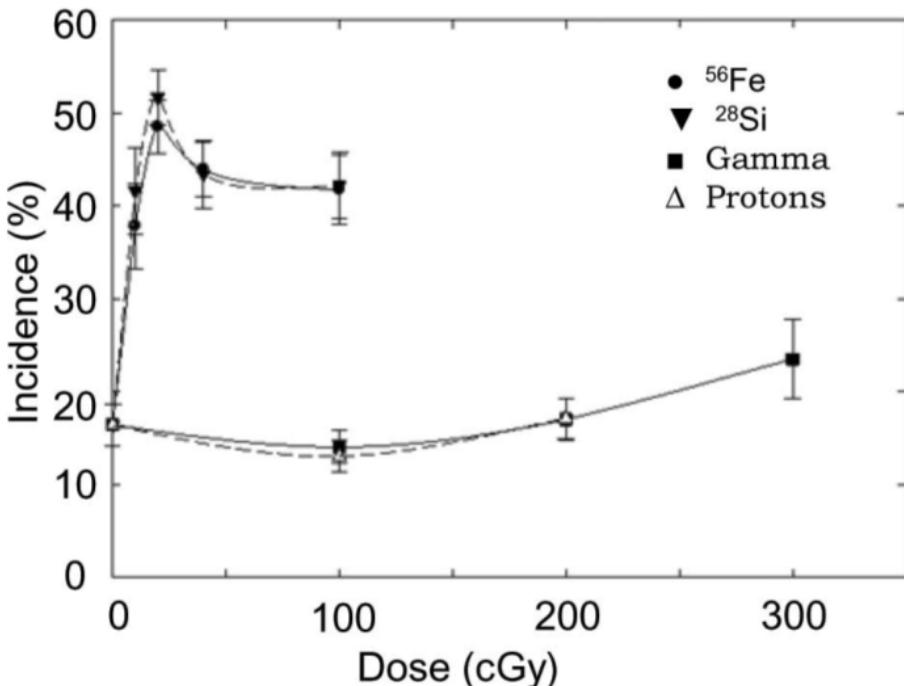
VI. Additional Comments regarding the ARS Risk Status Review

- The SRP still has concerns about defining the radiation risk from secondary radiation from whatever the final shielding will be. Rather than create a mixed field that mimics a deep space radiation mixed field it may be prudent to also add a mixed field based on the most likely shielding being considered. There was some hint in the documents provided that negative pions, and fast neutrons may be a significant component of these secondary's and these are known by radiobiologists to have relative biological effectiveness (RBEs) greater than one. It may be prudent to examine the known radiobiology and determine if further studies of these particles are needed to better define if they pose risks that might alter the approach to shielding being considered at the present time.

VII. Additional Comments regarding the Cancer Risk Status Review

The SRP would like to address two issues that are very important and they both apply to all of the current risks in the Space Radiation Program Element research plan. A summary of how this can be better addressed follows.

- It has been revealed in the carcinogenesis research, there is a huge variation in the incidence of HZE-induced tumors in mice depending on the specific strain of mice being tested.



This is the graph that was presented during the WebEx/teleconference (p. 96 of the 2014 Space Radiation Program Element presentation to the SRP: Weil et al. PLoS One. Aug 2014²). It refers to Mike Weil's HZE-induced liver tumors in C3H mice indicating an RBE of about 50-70 compared to gamma rays. Much hype has been made of these data. What was not shown in the presentation but was shown in another paper from Weil's group (Bielefeldt-Ohmann et al. Health Phys. Nov 2012³) is that when he repeated this study using BALB/c mice there were no liver tumors with any radiation. So, the elephant in the room is what RBE is NASA going to use to determine the risk for HZE-induced liver cancer? 50 or 1? This highlights the entire shortcoming of past and current NASA-funded carcinogenesis risk research – that is the problem of response differences between mouse strains. In the graph above the background incidence is nearly 20 tumors in unirradiated mice. Thus the C3H strain is predisposed to develop liver tumors. This represents another problem with most studies related to carcinogenic risk models currently employed for NASA's HRP. Many if not most investigators are using mouse strains that are predisposed to spontaneous tumors either naturally or due to genetic manipulation. NASA needs to come to grips with this issue if it is ever going to get an accurate assessment of risk. The SRP presumes the same issue applies to risks of CNS deficits and degenerative disorders. The SRP does not know what the solution is, but NASA needs to obtain some recommendations from the experts. Is the use of outbred mice the answer?

- The astronauts that ultimately go to Mars will be exposed to low doses of space radiation in a chronic manner (as mentioned in the WebEx/teleconference the dose rates would be approximately 1 mGy/day over three years). Unfortunately, the NASA Space Radiation Laboratory (NSRL) facility cannot even come close to mimicking this situation. Considering that current research is revealing the

possibility of an inverse dose rate effect, NASA must make some effort to address this problem.

A summary of specific approaches that could help clarify these results is as follows:

- The SRP notes the high incidence of cancer observed after exposure to high LET radiation in “specific” mouse models is intriguing and should provoke further studies on the actual mechanisms. Since the models in which this has been observed cannot be classified as “normal”, it is prudent to not interpret the results as “alarming” with regard to the putative carcinogenic potential of high LET radiation. However, they do pave the way for further studies within the task.
- The results clearly show that in certain genetic backgrounds high LET radiation can be highly carcinogenic – much more so than low LET radiation. It will be important to define the characteristics of these genetic backgrounds and the underlying mechanisms. General rules that go over specific mutations and address general modifications in the DNA damage response may be particularly useful in this regard.
- The high incidence of cancer may not be evident in a truly “wild-type” system and this is something the task will need to address systematically in *in-vivo* model systems. The definition of what is “normal” is likely to be here the main challenge.
- Evidence that the carcinogenic potential of high LET radiation may not be as high for “normal” individuals as the results of “specific” mouse models suggest, may be extracted from radiation therapy trials in humans. As part of such trials, several thousands of patients have been exposed to ¹⁴C beams in Germany, and particularly in Japan, for the management of diverse forms of cancer. All of these patients have received a few Gy's of high LET radiation in tumor-adjacent normal tissue. The incidence of cancer at the levels suggested by the above mouse data is likely to have a marked increase in the incidence of second malignancies in this cohort of patients. This possibility may be addressed by meta-analysis of disease progression and disease-free survival, including incidence of second cancers; this information is likely to be stored in the corresponding databases of patient follow-up. Such analysis is likely to be critical for the further shaping of this task.
- Staging of cancer will need to be included in the gaps.
- Additional cataracts studies should be influenced by the National Cancer on Radiation Protection and Measurements (NCRP) letter report that will be released in February 2015. This report will be examining low LET effects and dose limits for radiation workers in the U.S. While few comments about high LET exposures will be made, studies of high LET could be influenced by the conclusions of this report.

VIII. References

1. Chylack and Cucinotta. NASCA Report 2- Longitudinal Study of Relationship of

Exposure to SR and Risk of Lens Opacity. 2012 - Radiat Res v178 p25.

2. Weil MM, Ray FA, Genik PC, Yu Y, McCarthy M, Fallgren CM, Ullrich RL. Effects of 28Si Ions, 56Fe Ions, and Protons on the Induction of Murine Acute Myeloid Leukemia and Hepatocellular Carcinoma. PLoS One. 2014 Aug 15;9(7).
3. Bielefeldt-Ohmann H, Genik PC, Fallgren CM, Ullrich RL, Weil MM. Animal studies of charged particle-induced carcinogenesis. Health Phys. 2012 Nov;103(5):568-76.

IX. 2014 Space Radiation SRP Research Plan Reviews: Statement of Task for the Risk of Degenerative Tissue or Other Health Effects from Radiation Exposure

The 2014 Space Radiation Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist. The purpose of the SRP is to review the Risk of Degenerative Tissue or Other Health Effects from Radiation Exposure section of the current version of the HRP's Integrated Research Plan (IRP) which is located on the Human Research Roadmap (HRR) website (<http://humanresearchroadmap.nasa.gov/>). Your report, addressing each of the questions in the charge below and any addendum questions, will be provided to the HRP Chief Scientist and will also be made available on the HRR website.

The 2014 Space Radiation SRP is charged (to the fullest extent practicable) to:

1. Based on the information provided in the current version of the HRP's IRP, evaluate the ability of the IRP to satisfactorily address the Risk by answering the following questions:
 - A. Have the proper Gaps been identified to address the Risk?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the appropriate targets for closure for the Gaps been identified?
 - i) Is the research strategy appropriate to close the Gaps?
 - C. Have the proper Tasks been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are there any additional research areas or approaches that should be considered?
 - iii) If a Task is completed, please comment on whether the findings contribute to addressing or closing the Gap.
 - D. If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including, but not limited to, answering these questions:
 - A. Is the Risk addressed in a comprehensive manner?
 - B. Are there areas of integration across HRP disciplines that are not addressed that would better address the Risk?
 - C. Other
3. Based on the updates provided by the Element, please evaluate the progress in the research plan since the last SRP meeting.
4. Please comment on any important issues that are not covered in #1, #2, #3 or #4 above, that the SRP would like to bring to the attention of the HRP Chief Scientist and/or the Element.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the WebEx conference call.
2. Participate in a WebEx conference call on November 21, 2014 from 12:00 – 3:00 pm ET.
 - A. Discuss the 2014 Space Radiation SRP Statement of Task and address questions about the SRP process.
 - B. Receive presentations from the Space Radiation Element; participate in a question and answer session, and briefing.
3. Prepare a draft final report (approximately one month after the WebEx conference call) that contains a detailed evaluation of the current IRP specifically addressing items #1, #2, #3, and #4 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The Space Radiation Element and the HRP Chief Scientist will review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP within two weeks of receipt of the draft report. If any misunderstandings or errors of fact are identified, the SRP will be requested to address them and finalize the 2014 SRP Final Report as quickly as possible. The 2014 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the Space Radiation Element and also made available to the other HRP Elements. The 2014 SRP Final Report will be made available on the HRR website (<http://humanresearchroadmap.nasa.gov/>).

X. 2014 Space Radiation SRP Status Review (WebEx/Telecon): Statement of Task for the Risk of Acute and Late Central Nervous System Effects from Radiation Exposure, the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs), and the Risk of Radiation Carcinogenesis

The 2014 Space Radiation Standing Review Panel (SRP) will participate in a Status Review that will occur via a WebEx/teleconference with the Human Research Program (HRP) Chief Scientist, Deputy Chief Scientist and members of the Space Radiation Program Element. The purpose of this review is for the SRP to:

1. Receive an update by the HRP Chief Scientist or Deputy Chief Scientist on the status of NASA's current and future exploration plans and the impact these will have on the HRP.
2. Receive an update on any changes within the HRP since the 2013 SRP meeting.
3. Receive an update by the Element or Project Scientist(s) on progress since the 2013 SRP meeting.
4. Participate in a discussion with the HRP Chief Scientist, Deputy Chief Scientist, and the Element regarding possible topics to be addressed at the next SRP meeting

The 2014 Space Radiation SRP will produce a report/comments from this status review within 30 days of the 2014 update. These comments will be submitted to the HRP Chief Scientist and copies will be provided to the Space Radiation Program Element and also made available to the other HRP Elements. The 2014 SRP Final Report will be made available on the Human Research Roadmap public website (<http://humanresearchroadmap.nasa.gov/>).

XI. Space Radiation SRP Research Plan Review WebEx/Teleconference Participants

SRP Members:

Gayle Woloschak, Ph.D. (chair) – Northwestern University
Colin Hill, Ph.D. – University of Southern California
George Iliakis, Ph.D. – University of Duisburg-Essen Medical School
Bruce Lamb, Ph.D. – The Cleveland Clinic
Peter Liu, M.D. – University of Ottawa
Noelle Metting, Ph.D. – U.S. Department of Energy
Christina Meyers, Ph.D. – M.D. Anderson Cancer Center
Raymond Meyn, Ph.D. - The University of Texas M.D. Anderson Cancer Center

NASA Headquarters (HQ):

Bruce Hather, Ph.D.
Stephen Davison, Ph.D.

NASA Johnson Space Center (JSC):

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Zarana Patel, Ph.D.
Michele Perchonok, Ph.D.
Mark Shelhamer, Sc.D.
Susan Steinberg, Ph.D.
John Uri
Sherry Thaxton, Ph.D.
Mihrinan Whitmore, Ph.D.

NASA Langley Research Center (LaRC)

Lisa Simonsen, Ph.D.

National Space Biomedical Research Institute (NSBRI):

Graham Scott, Ph.D.

NASA Research and Education Support Services (NRESS):

Tiffin Ross-Shepard

XII. 2014 Space Radiation SRP Roster

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